Title: Mortality and Vaccination with COVID-19 Vaccines (VSD#1343)

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Lead site: Kaiser Permanente Southern California

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Aim: To assess mortality risk after receiving COVID-19 vaccines among members enrolled in VSD sites

1. BACKGROUND

COVID-19 disease, caused by the novel coronavirus (SARS-CoV-2), has infected 13 million and killed over 260,000 Americans as of November 27, 2020 (Johns Hopkins University, 2020). While social distancing, wearing face masks and improved hygiene education/procedures have helped to slow the disease transmission, they are impermanent and not curative. Effective and safe therapeutics and COVID-19 vaccines will eventually be required to contain the disease. Since the early pandemic in March 2020, scientists worldwide have been racing to find effective and safe vaccines for COVID-19. On November 18, 2020, Pfizer announced that Pfizer and BioNTech's vaccine BNT162 had a vaccine efficacy rate of 95% in participants without prior SARS-CoV-2 infection. Two days later, they submitted an application to the US Food and Drug Administration for an emergency use authorization for their COVID-19 vaccine. On December 11, 2020, FDA granted an Emergency Use Authorization (EUA) for Pfizer-BioNTech COVID-19 vaccine for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older (FDA-1, 2020). Another US pharmaceutical company, Moderna, also reported 95% vaccine efficacy for their COVID-19 vaccine. Moderna was granted an EUA for their COVID-19 vaccine on December 18, 2020 (FDA-2, 2020). These two mRNA-based vaccines require two shots, 21 days apart for Pfizer-BioNTech COVID-19 vaccine and 28 days apart for Moderna's vaccine. Janssen COVID-19 vaccine is a replication incompetent adenovirus vector vaccine that is administered as a single dose. It was granted an EUA on February 27, 2021 (FDA-3, 2021). It demonstrated 66% overall efficacy against symptomatic, laboratory-confirmed COVID-19, and 85% efficacy against moderate-to-severe COVID-19 occurring at least 28 days after vaccination. There are several other COVID-19 vaccine candidates that are in Phase 3 of their clinical development program. As additional COVID-19 vaccines are granted authorization or approval, we will incorporate them into the mortality analysis if sample size permits.

Although clinical trials showed that the two mRNA COVID-19 vaccines and the adenoviral vector vaccine were well tolerated with no serious safety concerns observed to date (Polack et al., 2020; Baden et al., 2021; FDA-3, 2021), serious rare adverse events may not be revealed in clinical trials even with more than 30,000 participants. Of all adverse events, death is the most severe form.

Despite the existence of rare cases of plausible risk of death following vaccination, very few studies had showed the association between modern vaccines and death (Miller et al., 2015). McCarthy et al (2013) showed that mortality rates among a VSD population were lower than that in the general U.S. population. McCarthy et al (2016) investigated the association between vaccination and death among individuals 9 to 26 years of age and found that the risk of death was not increased during the 30 days after vaccination. COVID-19 vaccines are new, and their risk profiles are unknown; thus, it is important to study their safety including possible association with elevated mortality risk not due to the novel coronavirus infection.

2. METHODS

2.1 Study population: Kaiser Permanente Southern California (KPSC) will lead this study. All VSD sites will be invited. We will clarify with sites what data sources they have available and how complete the data are from the various sources over time. Membership on the vaccination date or index date will be required. Our primary analysis will include adults 18 and above. As COVID-19 vaccines are granted authorization or approval in additional age groups, we will incorporate the additional age groups into the mortality analysis when sample size permits.

2.2 Outcome: The outcome of this safety study is mortality except COVID-19 related death. The rationale for excluding COVID-19 related death is that mortality increased substantially during the pandemic due to COVID-19. Without excluding COVID-19 related death, any potential safety concerns associated with COVID-19 vaccine and mortality would be masked by the protective effect of COVID-19 vaccine against COVID-19 related death.

We will identify death primarily using the inpatient/outpatient files. VSD sites are in the process of adding a new variable to the inpatient/outpatient files to capture deaths occurring in the hospitals and Emergency Department (ED). Inpatient/outpatient files capture date of death and discharge diagnoses. These data files are updated weekly. Because usually it takes about 10 weeks for data to settle due to hospital length of stay and claims, we will describe death data monthly during the first 3-6 months and quarterly thereafter. We will conduct interim analyses every six months. However, death data from inpatient/outpatient files may miss deaths occurring in other settings and/or outside of the health care system.

Our preliminary investigation of historical data from KPSC showed that inpatient and ED deaths only accounted for about 30% of all deaths among active members and those members who died within 90 days after disenrollment. We propose to ask participating VSD sites to create a death ancillary file to collect more death data from patients' records in the electronic medical records (EMR) and membership files which capture reported deaths outside of medical settings and are more timely than the annual state death file. At KPSC, among deaths of active members occurring in 2018 reported in the C2019 Mort file, the deaths identified through inpatient/ED encounters and the ancillary file (i.e., deaths reported to member services) accounted for 94% of the total deaths. Thus, these sources capture a substantial portion of deaths without relying on the annual state death files. This death ancillary file will be updated monthly. We will combine this ancillary file with the inpatient/outpatient files monthly. In addition, we will also consider other death data sources including VSD mortality files. VSD mortality files include cause and date of

death among all members. Because the VSD mortality files are updated annually, we will merge the VSD mortality files with inpatient/outpatient files on an annual basis to capture additional death data. However, because the death data from the VSD mortality files are lagged by almost two years, they won't be used until the third year of the study. KPSC will explore the possibility of obtaining monthly updates of California's state death records and evaluate their data quality and data lag. We will assess whether other VSD sites have access to state death data and how frequently these data are updated.

To detect possible bias from inadequate confounding adjustment, we will conduct exploratory negative-control-outcome analyses separately for each of the COVID-19 vaccines (Shi et al., 2020). Trauma or injury hospitalization has been used as a negative control outcome in investigating the protective effect of influenza vaccination against influenza hospitalization and all-cause mortality in the elderly (Jackson et al., 2006). Trauma or injury hospitalization was selected as a control outcome because it should be unrelated to influenza infection. The authors found that influenza vaccination appeared to be protective against both influenza hospitalization and all-cause mortality as well as trauma or injury hospitalization, indicating inadequate confounding adjustment. We will use trauma or injury hospitalization after COVID-19 vaccination as a negative control outcome for this study. We will identify trauma or injury hospitalization with the following ICD-10 codes: S00-T88 for injury, poisoning and certain other consequences of external causes, and V00-Y99 for external causes of morbidity (CMS, 2021).

2.3 Exposure and risk windows: The emerging COVID-19 vaccines in the US include two mRNA-based vaccines, Moderna COVID-19 vaccine and Pfizer-BioNTech COVID-19 vaccine, and the adenoviral vector Janssen COVID-19 vaccine. There are other COVID-19 vaccine candidates in clinical development. Separate analyses will be conducted for each authorized/licensed COVID-19 vaccine, provided there is sufficient uptake at VSD sites.

We will not pre-specify the risk window for this study. We will employ a flexible analytic approach that allows for assessing mortality risk for certain days after exposure such as 21, 30 days or 42 days. The maximum follow-up is 3 years in this study. For details, please see our analytic plan below.

2.4 Comparators: Two concurrent comparison groups will be used depending on stages of surveillance. At early and middle stages of surveillance (e.g., less than 60% of the population is vaccinated with COVID-19 vaccine), our primary comparison group will be those who were not vaccinated with a COVID-19 vaccine prior to the date of an interim analysis (for details about the interim analyses, please see below). Those who received a COVID-19 vaccine will be in the exposed group in analyses. To make the unexposed comparator group like the exposed group, we will consider the following members: those who did not receive any COVID-19 vaccine but had ≥1 dose of influenza vaccine within the two years prior. Confounder adjustment is critical in using unvaccinated comparators. For details about how to adjust for confounders, please see our analytic plan.

At later stages of surveillance (e.g., more than 60% of the population is vaccinated with COVID-19 vaccine), we will consider using those early vaccinees who received a COVID-19 vaccine at

least 6 months prior to an interim analysis date. The reasons for using this comparison group are 1) fewer comparable unvaccinated individuals will be available as most of the population will have received a COVID-19 vaccine; 2) it will help to increase the sample size of the comparison group over time. In this design, those who received a COVID-19 vaccine recently will be in the exposed group while early vaccinees will be comparators. Early vaccinees can contribute person time to both the risk window and the comparison window. The limitations of this approach are 1) given the prioritization scheme, early vaccinees may be systematically different from those who are vaccinated later, and thus, this comparison group may not be comparable to the exposed group; 2) the loss to follow-up will differ between recent vaccinees and early vaccinees because increasing time since vaccination will increase the likelihood of disenrolling from health plans; 3) if the elevated mortality risk of a COVID-19 vaccine is constant over several years after vaccination, this method would not detect the risk because it compares the recent risk versus long term risk; 4) the comparison window must occur after the risk window; however, the exact risk window for these new vaccines are unknown; 5) potentially, immortal time bias may be introduced because one has to survive up to an interim analysis to be included in that interim analysis.

The design using either of these two concurrent comparison groups will be influenced by data lag. However, if the data lag is non-differential between the exposed group and the comparison group, the point estimate of vaccination association with mortality will be unbiased, but with wider 95% confidence intervals because the number of deaths will be undercounted.

We will not consider historical comparison approach because we anticipate that this design will be impacted by data lag significantly. Historical death data will be more complete than the death data for the current population; thus, point estimate of vaccination association with mortality will be underestimated, potentially resulting in a false negative signal.

The self-controlled case series (SCCS) design is not appropriate here because the outcome (death) prevents one from future exposure and the outcome is not a recurrent event (Farrington 1995). Data lag also has impact on estimating the association between vaccination and death, because deaths in the comparison window are more likely to be undercounted than deaths in the preceding risk window. In addition, a SCCS design requires a pre-specified risk window for death which is unknown.

2.5 Analytic plan

We plan to provide quarterly mortality reports by vaccine type, dose number, age, sex, and race/ethnicity using two approaches: a matched cohort analysis and a cohort analysis with a time-varying exposure. In the matched cohort analysis, follow-up will start at a vaccination date for vaccinees or at an index date for comparators. A frequency matching approach will be employed to use the distribution of vaccination week of the first dose among vaccinees to assign the index date to unvaccinated comparators who had ≥1 dose of influenza vaccine within the two years prior to the reporting month; follow-up for the first dose will be censored upon the receipt of the second dose. Follow-up will end if patients die, disenroll, receive a COVID-19 vaccine for unvaccinated individuals, or at the end of the current report. Mortality rates per 100 person-years

will be calculated after the first and the second doses among vaccinees and after the index date among comparators. In a cohort analysis with a time-varying exposure, a patient's follow-up up to the current month is partitioned into three intervals: a comparison interval before the first vaccination, an interval after the first dose and before the second dose if the second dose is received, and an interval after the second dose. Those who have not received COVID-19 vaccines will only contribute to the comparison interval. Mortality rates per 100 person-years will be calculated for these three intervals. We will report the number of deaths, mortality rates, and relative risks cumulatively up to the reporting month. Due to data lag in deaths from other settings (e.g., from claims and outside utilization of VSD sites) and in COVID-19 vaccination outside of VSD sites, we will include those who were vaccinated at least two months prior to the reporting month. Those comparators who were vaccinated during the subsequent two months will be censored upon receipt of their first dose of COVID-19 vaccine. In a sensitivity analysis using the matched cohort design, we will calculate mortality at 30 days after the index date among comparators, and 30 days after the first and second doses among vaccinees.

We will conduct interim analyses every six months for a total of 6 interim analyses over 3 years. Although we will not establish and apply stopping rules as in a formal sequential analysis, we will adjust for multiple testing using the Pocock approach for controlling overall type I error rate (Pocock, 1982). Compared to O'Brien-Fleming approach, with constant significance levels, the Pocock approach allows for early signal detection if there exists an association between the vaccination and mortality. A diagram for the interim analyses is displayed in Figure 1.

In our primary analyses, we will include all deaths except COVID-19 related deaths. We will use cause of death, if available, to identify COVID-19 related deaths. When cause of death is not available in the early stage of surveillance, a death will be designated as a COVID-19 related death if it is identified from inpatient or ED settings with a COVID-19 diagnosis code or a positive lab test within 30 days of death. We will conduct two secondary analyses. First, we will include all-cause deaths. In this secondary analysis, the association between COVID-19 vaccines and mortality will be affected by both any potential adverse effect of the vaccine on mortality and any protective effect of the vaccine against mortality by reducing SARS-CoV-2 infection and severity of COVID-19 disease. Second, we will exclude deaths due to external causes such as accident and homicide in addition to excluding COVID-19 related deaths (McCarthy et al, 2016).

Survival analyses will be carried out to assess the mortality risk of COVID-19 vaccines. The start time (index date) for the exposed group is the date that one received the first dose of COVID-19 vaccine. We will assign an index date to each comparator according to the frequencies of COVID-19 vaccination dates in each month of the six months of an interim analysis. To reduce selection bias, we will employ a propensity score approach to adjust for the potential imbalance in confounders between the exposed and the comparison groups. Our primary analyses will use an improved inverse propensity weighting: stabilized weights (SW) (Robins et al, 2000). The stabilized weights not only reduce the impact of some extreme weights but also preserve the original sample size (Xu et al, 2010).

Let t_k denote the calendar time for the kth interim analysis, t_k =6, 12, 18, 24, 30, and 36 months after start of surveillance for k=1 to 6. At the kth interim analysis, two steps will be taken. When the pool of the first comparison group becomes limited, we will consider those who are vaccinated more than 6 months prior to the kth interim analyses to be comparators in the kth interim analysis.

Step 1: We will use logistic regression models to calculate propensity scores for those who are newly identified in the exposed and the comparison groups. We will identify those who were vaccinated with a COVID-19 vaccine between $t_{(k-1)}$ and t_k and those comparators whose index dates were between $t_{(k-1)}$ and t_k but had never been vaccinated with a COVID-19 vaccine. Let n_{1k} represent the sample size of the exposed group and n_{0k} represent the sample size of the comparison group, $N_k = n_{1k} + n_{0k}$ is the sample size at the kth interim analysis. A propensity score model will be built with the exposure variable as the dependent variable. We will include the following confounders in our propensity score models: seasonality, age, gender, race/ethnicity, socioeconomic status (SES) variables such as Medicaid status and neighborhood level income and education, comorbidities, pregnancy status, health care utilization (e.g. number of outpatient, ED and inpatient visits) in prior year, receipt of other vaccines, VSD site, and etc. We will also collect the information whether a patient has ED and inpatient visits one week prior to the index date. Comorbidities are important confounders. It is likely that the exposed and the comparison group will differ in comorbidities. We will explore three ways to use comorbidities as predictors for vaccination in the propensity score models: 1) using each individual comorbidity; 2) using Charlson comorbidity index (CCI); and 3) using the more sophisticated Elixhauser Comorbidity Index (ECI). We will choose the one that is the best predictor in propensity score models and is balanced between the exposed and comparison groups after stabilized weights are applied.

We will then use the results from the propensity score model to calculate SW for each individual. Individuals in the exposed group will carry their SWs for future interim analyses. Those in the comparison group will carry their SWs for future interim analyses until they become vaccinated with COVID-19 upon which they will be in the exposed group. We will examine whether the SWs help balance confounders among treatment groups. If necessary, we will trim data to optimize SWs.

Step 2: We will employ a cumulative estimation approach to assess the mortality risk of the vaccines using all data up to t_k, the time for the kth interim analysis (Xu et al 2016). The sample size for the kth interim analysis will be sum of $N_1,\ldots, N_k$. Those in $N_{(k-1)}$ will be allowed to extend their follow-up into t_k. For vaccines that require only one dose such as Johnson & Johnson's JNJ-78436735, a proportional hazard model will be fit to assess the association between COVID-19 vaccines with mortality (Cox 1972; Cox 1975). The assumption of proportional hazard will be tested using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals (Schoenfeld 1982; Harrell and Lee, 1986). If the assumption does not hold, we will include an interaction term between the exposure variable and time in the Cox model to allow the exposure effect to vary over time (Cox and Oakes 1984; Allison 1995).

For the two mRNA-based vaccines that require two doses, the counting process approach will be used with a new observation period when the second dose starts (Andersen and Gill, 1982; Andersen et al, 1992). The index date is still the date of receipt of the first dose. Different indicator variables will be used for the first and the second doses. This counting process approach can be used to test if the mortality risk after receiving the second dose differs from the risk after receiving the first dose. In these survival analyses, SW will be applied to adjust for imbalance of confounders between the exposed and the comparison groups (Xu et al 2012; Xu et al 2014).

As we mentioned previously, we won't pre-specify the risk window for these new vaccines. However, our approach can assess the mortality risk by different risk windows. For example, when we censor follow-up at 42 days after vaccination, we will be able to assess mortality risk within 42 days after vaccination. This is equivalent to assessing a vaccination effect with a risk window of 42 days using either SCCS design or a risk-interval design (Glanz et al 2006).

In addition to conducting separate analyses for each COVID-19 vaccine, we will also consider comparing different vaccines to each other when uptake of two or more vaccines is sufficient to allow for such a comparison. We will use the analytic approaches described above for this purpose. On the other hand, since mortality is expected to be a rare adverse event, at the initial phase of vaccination rollout, we may combine the two mRNA vaccines to increase the sample size and statistical power.

We will employ a similar analytic approach as for the primary outcome in the exploratory negative control outcome analyses. Because the protective effect of COVID-19 vaccines against death was similar for doses 1 and 2 of mRNA vaccines, we will compare vaccinated individuals and comparators in the negative-control-outcome analyses and will not examine if the protection effect of COVID-19 vaccines against Trauma or injury hospitalization differs by dose for mRNA vaccines. We will estimate stabilized weights from propensity score models where the same covariates for the primary outcome will be included, and the receipt of COVID-19 vaccination will be the dependent variable. We will analyze time from receipt of the first dose among vaccinees or the index date among comparators to an incident hospitalization for trauma or injury in survival analyses with and without applying SWs.

3. STUDY LIMITATIONS

There are some potential limitations in our proposed approach. First, important confounders may not be available. The validity of this observational study may be threatened without adjusting for these unmeasured confounders. Second, this study does not address if the mortality risk of COVID-19 vaccines differs by gender, age, race/ethnicity, and/or clinical conditions although these risk factors will be adjusted for in propensity score models. Third, to some degree, the validity of our results depends on the completeness and accuracy of ascertainment of deaths in our death data. Some patients who appear alive in VSD data may have died while some patients who appear to have died in VSD data may be still alive. In addition, we observed that a small proportion of patients who appear to have died in VSD data had medical visits after death. Fourth, using a COVID-19 diagnosis code or a positive lab test within 30 days of death to

identify and exclude COVID-19 related death may result in misclassification; however, this approach is needed because data on the true underlying causes of death are not available in a timely fashion. We recognize the potential for misclassification of COVID-19 related death, and as such will include all-cause deaths in the secondary analysis approach.

4. DATA SOURCES

We will use the VSD Dynamic Data Files (DDF) and cycle files from all participating sites. We will also be requesting that sites generate an ancillary death file. The data files will be updated monthly with death data from patients' records in the electronic medical records (EMR) and membership files. Necessary files include the Constant File, Enroll File, Vaccine File, Inpatient File, Outpatient File, Procedure file, Mort and MortCOD Files, Medicaid and Geocode files, Pregnancy Episode Algorithm (PEA), Dynamic Pregnancy Algorithm (DPA), and Pregnancy files, and COVID-19 DXID and lab files. The files will include but are not limited to the following variables: age, sex, race/ethnicity, SES variables, VSD site, comorbidities, pregnancy status, health care utilization, receipt of influenza and other vaccines, and vital status.

5. DATA MANAGEMENT

SCK will be responsible for overall data management activities. SCK will oversee study documentation and archiving. Data will be
exchanged using the secure Distributed Data Model (DDM). Participating sites will be responsible for exploring and sharing information about availability of their death data, investigating any data quality issues, and incorporating additional data sources or data elements. SCK will create a data dictionary and instructions for ancillary files as needed, and sites will write and test the programs that will be used to create these files according to the data dictionary and instructions. SCK programmers/analysts will write and test the programs that will be used to capture the data from the DDF and ancillary files at the participating sites. Individual level data will be collected to calculate propensity score weights and conduct survival analyses.

6. CHART REVIEW

Manual review of medical records will be performed to assess cause of deaths that occurred in the health care systems of participating sites. This information will be used to determine if a death is due to external causes such as accident and homicide. Clinician input may be required to assess biological plausibility of identified cause of death being vaccine related. All deaths within 42 days after vaccination will be chart reviewed. When the number of deaths in the comparison group is large, a random sample will be selected for chart review.

We will also conduct manual reviews of a random sample of medical records to evaluate the quality of death data. For example, deaths identified from claims with encounters after the death date, or death dates occurring prior to vaccination, are suspect and warrant further chart review. Because the proportion of deaths from various sources and their accuracy may differ by site, each site will conduct reviews of a random sample of medical records and site-specific confirmation rates will be obtained. The confirmation rates of deaths may be used in a sensitivity analysis.

We plan to adapt and utilize the chart abstraction forms and manuals used in previous VSD studies as needed for this project. Participating sites will have the opportunity to review the tools. We will send the abstraction forms to CDC for review and comment before the documents are finalized. We will coordinate the collection, analysis, and interpretation of chart abstraction data. Chart review data will be collected from participating sites in Excel or REDCap.

7. SITE RESPONSIBILITIES

We hope that all sites with appropriate data will participate. Participating VSD sites are responsible for obtaining site-specific IRB approval and data use agreements, if applicable. Data managers at each site may be asked to create ancillary files and review the SAS program(s) prior to submission to the DDM. CDC will be responsible for submitting programs to the DDM. Participating sites and CDC will be invited to provide feedback on study results, manuscripts, and presentations.

8. HUMAN SUBJECTS

The privacy and confidentiality of all study subjects will be strictly protected, according to standard VSD procedures. We will seek IRB review and approval at each individual participating VSD site. We will also request a waiver of HIPAA authorization, as this study will involve only a limited dataset of protected health information (PHI). Data use agreements will be signed with all participating sites.

PROJECTED TIMELINE

Date	Description
December 2020	Present protocol on VSD Project Call
January 2021	Provide a final protocol to CDC for approval
January 2021	Invite sites to participate and obtain necessary IRB approvals and DUAs
January 2021 - March 2021	Ancillary death file development by participating sites. DDM SAS program development by KPSC and distribution to participating sites for review and approval.
March 2021	Preliminary data extraction
March 2021	Begin monthly updates of ancillary death file
April-October 2021	MMWR paper preparation and publication
March 2022	Present findings from first interim analysis
October 2022	Present findings from second interim analysis
April 2023	Present findings from third interim analysis

October 2023	Present findings from fourth interim analysis
April 2024	Present findings from fifth interim analysis
October 2024	Present findings from final analysis
TBD	Manuscript development

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FDA-3. Janssen COVID-19 Vaccine EUA Letter of Authorization. Accessed on March 2, 2021. https://www.fda.gov/media/146303/download

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Number represents subject;
letter **v** denotes vaccination with a COVID vaccine;
letter **p** denotes having a preventive care but not COVID vaccines;
PS: propensity score model

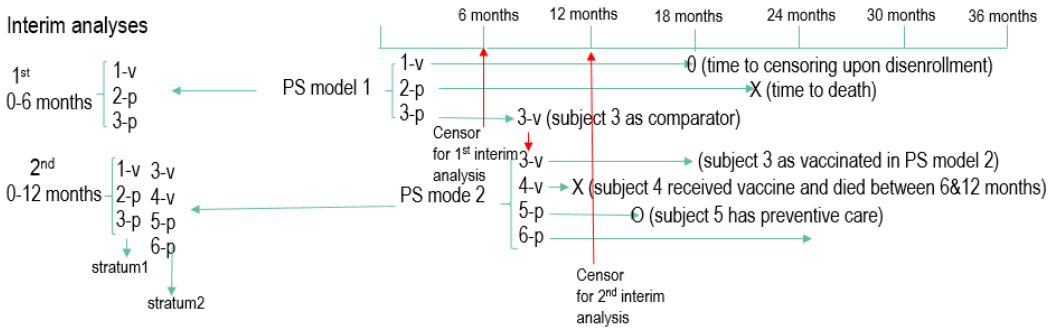

Figure 1. Overview of interim analyses